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| 10/567,470 | 11/30/2006 | Patrick L. Iversen | 120178.422USPC | 4986 |

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| EXAMINER | |
|---|---|
| ANGELL, JON E | |

| ART UNIT | PAPER NUMBER |
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| 1635 | |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/567,470 | IVERSEN, PATRICK L. | |
| | Examiner | Art Unit | |
| | J. E. ANGELL | 1635 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *02 February 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-7,13-21 and 27-29* is/are pending in the application.

4a) Of the above claim(s) *14-21 and 27-29* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7 and 13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *See Continuation Sheet*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Attachment(s) 3). Information Disclosure Statement(s) (PTO/SB/08), Paper No(s)/Mail Date :11/30/06, 10/14/08, 02/13/09, 04/13/09, 05/26/09, 08/31/09 .

## DETAILED ACTION

This Action is in response to the communication filed on 02/10/2010.

The amendment filed 02/10/2010 is acknowledged and has been entered.

Claims 1-7, 13-21, 27-29 are currently pending in the application and are addressed herein.

### *Election/Restrictions*

Applicant's election with traverse of Group I and the species: flaviviridae and SEQ ID NO: 7 in the reply filed on 2/10/2010 is acknowledged. The traversal is on the ground(s) that the target sequences are linked by a special technical feature (targeting a stem loop structure in the 3'-treminal end 40 bases of the negative-sense RNA strand of *flavivirus*. This is not found persuasive because the asserted special technical feature does not make a contribution over the prior art for the reasons set forth herein (see rejections below). Therefore, there is no special technical feature linking the claims and the requirement is still deemed proper and is therefore made FINAL.

Claims 14-21, 27-29 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected Invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 02/10/2010.

Claims 1-7 and 13, drawn to the elected species, are examined herein.

### *Information Disclosure Statement*

1. The information disclosure statements (IDS) submitted on 11/30/06, 10/14/08, 02/13/09, 04/13/09, 05/26/09, 08/31/09 are acknowledged. The submissions are in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statements are being considered by the examiner.

### *Claim Rejections - 35 USC § 103*

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. Claims 1-7 and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Anderson et al. (U.S. 6,391,542) in view of Schuster et al. (J. Virol. (2002), vol. 76(16), pages 8058-8068) and Stein et al. (WO 2003/033657, of record).

The instant claims encompass an oligonucleotide analog compound for use in inhibiting replication in mammalian host cells of an RNA virus having a single-stranded, positive-sense RNA genome from the Flaviviridae family and characterized by: (i) a nuclease resistant backbone, (ii) capable of uptake by mammalian host cells, (iii) containing between 12-40 nucleotide bases, (iv) having a targeting sequence of at least 12 subunits that are complementary to a region associated with stem-loop secondary structure within the 3'-terminal end 40 bases of the negative sense RNA strand of the virus, and (v) capable of forming a heteroduplex structure

with the negative strand viral *ssRNA* genome having a Tm of at least 45°C and disruption of said stem-loop secondary structure (see claim 1).

Anderson et al. teach an antisense oligonucleotide sequence for inhibiting the replication in mammalian host cells of an RNA virus having a single-stranded, positive-sense RNA genome from the Flaviviridae family (HCV) wherein the oligonucleotide compound is capable of uptake by mammalian cells, contains 21 nucleotides that are complementary to a region associated with a stem-loop secondary structure within the 5'-terminal end 40 bases of the positive (+) RNA strand of the virus (e.g., see Table 1, SEQ ID NO: 7; column 5, lines 23-55; etc.). Regarding the 5'-terminal stem-loop, Anderson teaches:

> "The 5' untranslated region (5' UTR) or 5' noncoding region (5' NCR) of HCV consists of approximately 341 nucleotides upstream of the polyprotein translation initiation codon. A hairpin loop present at nucleotides 1-22 at the 5' end of the genome (HCV-1) identified herein as the "5' end hairpin loop" is believed to serve as a recognition signal for the viral replicase or nucleocapsid proteins."

Anderson et al. do not teach an oligonucleotide compound that targets a stem-loop structure in the 3'-terminal 40 nucleotides of the negative (-) RNA strand of the virus or that the oligonucleotide is composed of morpholino subunits linked by uncharged intersubunit linkages as required by the claims.

However, Schuster et al. teach that the positive (+) RNA strand of HCV is used to synthesize the negative (-) strand of the virus which is complementary to positive (+) strand (e.g., see first paragraph of reference). Schuster also teaches that the negative strand comprises a stem-loop structure within the 3'-terminal 40 nucleotides and that the 3'-terminal 40 nucleotides are identical to instant SEQ ID NO: 7 (e.g., see Figure 2a, SL-AI). Furthermore, Shuster also specifically teaches:

> "The 3' end of the HCV (-) strand RNA is the strict antisense sequence of the (+) strand IRES. It is therefore of particular interest to compare both structures, which could adopt mirror image conformations. The first stem loop in the (-) strand RNA, SL-AI, is indeed the mirror image of domain in the IRES." (See page 8066, second paragraph under "DISCUSSION"); and,
>
> "It is noteworthy that in vitro replication studies performed with recombinant NS5B showed that the minimal RNA fragment required for efficient replication of the (-) strand spans nt -239 to -1 (43), which corresponds to the domain I identified in the present study. This strongly suggests that the replication complex may recognize a stable structure at the 3' end of the RNA molecule. This hypothesis is further supported by the fact that unstructured homopolymeric RNAs are poor templates for de novo initiation of RNA synthesis (24). In addition, a specific interaction between domain I and the HCV nonstructural protein NS3 was reported last year (1). The first stem-loop, SL-AI, and in particular the run of guanosines in the stem, were absolutely required for this interaction. Recently, Friebe et al. (15), using an adapted replicon system, developed the first test allowing replication in vivo to be followed. They showed that the presence of the entire IRES region was required for maximal replication efficiency. In these experiments, the involvement of the IRES in translation was dissociated from its role in the replication process. Once transcribed to give rise to the 3' (-) end of the minus strand, the nucleotides encoded by the IRES sequence are involved only in the replication process of the virus. In addition, the authors showed that the region encompassing nt -125 to -1 also supported significant replication. Accordingly, a functional subdomain encompassing SL-AI and SL-BI may represent the minimal initiation site for (+) strand RNA synthesis." (See page 8067, first full paragraph).

Therefore, in summary, Schuster et al. teach that (1) 3' negative (-) strand is the strict antisense of the (+) strand, (2) the domain I of the 3'-negative (-) strand is required for efficient replication, (3) SL-AI (the first stem loop of the 3' negative (-) strand) is absolutely required for NS3 interaction, and (4) SL-AI may be part of a minimal initiation site for (+) strand synthesis.

Furthermore, Stein et al. teach antiviral compounds directed against an RNA virus from the flavivirus family. The antiviral compound comprises a substantially uncharged oligomer having (a) a sequence of 12 to 40 subunits, supporting a targeting base sequence that is substantially complementary to a viral target sequence which spans the translation initiation region of said first open reading frame, and (b) a substantially uncharged backbone. In a

preferred embodiment, the oligomer is a morpholino oligomer, having a sequence or morpholino subunits. The subunits are generally connected by uncharged, phosphorus-containing intersubunit linkages, which joining the morpholino nitrogen of one subunit to the 5' exocyclic carbon of an adjacent subunit. In one embodiment, these linkages are phosphorodiamidate linkages. The substantially uncharged oligomer will typically have a Tm, with respect to binding to the viral target sequence, of greater than about 45 C, as well as an ability to be actively taken up by mammalian cells. In addition, the compound can generally be recovered, in a heteroduplex form consisting of the oligomer and a complementary portion of the viral genome of the RNA virus.

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Anderson et al., Schuster et al. and Stein et al. to create the claimed invention with a reasonable expectation of success. That is, it would have been prima facie obvious to an ordinary artisan to modify the teaching of Anderson et al. such to make an oligonucleotide compound targeted to the first stem-loop structure in the 3'-terminal 40 nucleotides of the negative (-) RNA strand of the HCV wherein the oligonucleotide is targeted to a sequence having SEQ ID NO: 7. Furthermore, it also would have been prima facie obvious to an ordinary artisan to modify the oligonucleotide compound such that it is composed of morpholino subunits linked by the uncharged intersubunit linkages as taught by Stein et al. (and required by the claims).

The motivation to target the stem-loop structure in the 3'-terminal 40 nucleotides of the negative (-) RNA strand is provided by Schuster et al. who teaches that it is required for efficient replication of the virus. Additionally, Stein et al. provides the motivation for making the

structural modifications to the oligonucleotide by indicating that the modifications result in a more efficient oligonucleotide inhibitor.

***Conclusion***

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. E. ANGELL whose telephone number is 571-272-0756. The examiner can normally be reached on Monday-Thursday 7:00 a.m.-5:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's acting supervisor, Fereydoun Sajjadi can be reached on 571-272-3311. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/J. E. ANGELL/
Primary Examiner, Art Unit 1635